Haemophilia patients' unmet needs and their expectations of the new extended half-life factor concentrates.

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Abstract: INTRODUCTION: National Member Organisations (NMO) of persons with haemophilia (PWH) from the DACH Region (D = Germany, A = Austria, CH = Switzerland) were interested to better understand PWH's expectations and concerns of extended half-life (EHL) factor concentrates (FC) before availability in these countries. METHODS: Based on an expert meeting and focus groups conducted across Germany a survey for haemophilia patients and their parents was developed and was sent out to 2,644 PWH. RESULTS: One thousand and seven questionnaires were sent back (38.1%); 743 adults and 262 parents. Most patients had haemophilia A (84.5%), were severely affected (73.7%), received prophylaxis (57%) and used recombinant FC (60.2%). One-quarter did not know the correct half-life of their FC [HA/FVIII: 26%, HB/FIX: 31.1%]. Four percent were unsatisfied with their current FC, mainly with short half-life of FC and difficult manageability. They expected from new EHL products less frequent injections (55.2%), better efficacy (32.1%) and safety/no side effects (15.7%); 59.5% would be willing to switch to new products if they have a prolonged half-life and the same safety of the current FC. They wish more information about half-life (84.4%), possible side-effects (81.3%) and efficacy (77%) and wanted to receive information about new products from their haemophilia treater (76.3%) and the newsletter of their NMO (74.3%). Significant differences across countries were found. CONCLUSIONS: The representative survey could show that although PWH were generally satisfied with their current FC, the majority would be willing to switch to EHL products assuming half-life is prolonged and has the same safety of the current FC.

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Haemophilia patients' unmet needs and their expectations of the new extended half-life factor concentrates

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Introduction: National Member Organisations (NMO) of persons with haemophilia (PWH) from the DACH Region (D = Germany, A = Austria, CH = Switzerland) were interested to better understand PWH's expectations and concerns of extended half-life (EHL) factor concentrates (FC) before availability in these countries. **Methods:** Based on an expert meeting and focus groups conducted across Germany a survey for haemophilia patients and their parents was developed and was sent out to 2,644 PWH. **Results:** One thousand and seven questionnaires were sent back (38.1%); 743 adults and 262 parents. Most patients had haemophilia A (84.5%), were severely affected (73.7%), received prophylaxis (57%) and used recombinant FC (60.2%). One-quarter did not know the correct half-life of their FC [HA/FVIII: 26%, HB/FIX: 31.1%]. Four percent were unsatisfied with their current FC, mainly with short half-life of FC and difficult manageability. They expected from new EHL products less frequent injections (55.2%), better efficacy (32.1%) and safety/no side effects (15.7%); 59.5% would be willing to switch to new products if they have a prolonged half-life and the same safety of the current FC. They wish more information about half-life (84.4%), possible side-effects (81.3%) and efficacy (77%) and wanted to receive information about new products from their haemophilia treater (76.3%) and the newsletter of their NMO (74.3%). Significant differences across countries were found. **Conclusions:** The representative survey could show that although PWH were generally satisfied with their current FC, the majority would be willing to switch to EHL products assuming half-life is prolonged and has the same safety of the current FC.

Keywords: DACH Region, expectations, extended half-life, haemophilia, long-acting factor concentrates, patients' needs, survey

Introduction

Most haemophilia patients in Western Europe nowadays have the opportunity to get regular prophylaxis [1] and can live normal lives due to the sufficient availability and funding of plasmatic and recombinant factor concentrates (FC) [2,3]. Several studies have shown the advantages of prophylaxis over episodic therapy. In young children prophylaxis could prevent joint damage compared to episodic treatment [1,4,5]. Adult patients on prophylaxis showed significantly less physical pain, had better general health, less severe bleeds, less disease progression, and reported significantly better health-related quality of life compared to those on episodic treatment [6,7]. The aim of regular prophylaxis is to maintain factor levels ≥1% [8]. But there is no clear correlation between trough levels and bleeding events as some persons with haemophilia (PWH) bleed with trough levels >1%, while others experience no bleeds with trough levels <1% [9]. Therefore, trough levels are at least as important as other parameters such as clinical outcomes to find the optimal treatment regimen. Regular factor VIII concentrates have short half-lives of in average 12 h [10], although there is a high inter-individual variability (6–29 h) [11,12]. Therefore, the majority of

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haemophilia A (HA) patients inject themselves every other day to three times per week [8]. With an average factor IX half-life of 18–24 h most haemophilia B (HB) patients inject themselves twice per week [13]. It could be demonstrated that the burden of frequent injection with the regular existing FC was one of the major obstacles to adherence in adolescents and adults [14,15]. In younger children, administration of FC is particularly demanding. Children have often difficult venous access, parents may be reluctant to administer the FC to the own child, and the reconstitution and administrations in the morning before school and going to work may become very stressful. Moreover, it was shown that caregivers who spent more than 8 h for injecting their haemophilic children in the previous month perceived a greater burden [16]. Poor treatment adherence can lead to increased annual bleeding rate (ABR) [9,17]. Last, but not least adherence was shown to be correlated with age of haemophilia patients [18,19].

The new, up-coming extended half-life (EHL) FC for treatment of HA and HB may have the potential to reduce injection frequency, to increase protection and to improve patients' quality of life [20–23]. Little is known about patients' perspectives on the use of these new FC [24] and their willingness to switch to these products.

The role of the national member organisations (NMO) of haemophilia patients is to support and advise their members, e.g. concerning novel therapies, to facilitate access to treatment, to provide patients' perspectives and to inform the general population about haemophilia. They are voluntary groups where everybody with interest in bleeding disorders can become a member. The number of families with haemophilia in the NMOs varies with respect to the total haemophilia population across the countries. In Germany there are 1,499 haemophilia members representing approximately 18.3% of the expected national haemophilia population, in Switzerland 404 (50.5%), and in Austria 487 (57.5%), respectively.

National Member Organisations of the DACH Region (D = Germany, A = Austria; CH = Switzerland) were interested to better understand what patients already know about the new FC with EHL, if there is a real need for these FC in the haemophilia community and to what extent PWH would switch to these new products. Furthermore, the patient organisations wanted to learn about the PWHs expectations and concerns about these new FC in order to adapt their support for the haemophilia community.

Study design and methods

The study consisted of two phases: (i) conduct of an expert meeting and separate focus groups with adult haemophilia patients and parents of haemophilic children in order to gather some insight into patients' expectations of new EHL FC and their unmet needs; (ii) systematic postal survey among all registered members with HA or HB of the NMOs of the DACH Region.

Expert meeting

An expert meeting was performed with representatives of the German NMO and a leading haemophilia treater in order to discuss the study outline and the questions for the focus groups.

Focus groups

Five separate focus groups with adult haemophilia patients and parents of children with haemophilia were conducted regarding new EHL products. Focus groups were based on semi-structured interviews (lasting 1.5–2 h each) and contained 12 questions concerning patients' current treatment, information about treatment options and how products are chosen. Focus groups took place across Germany in Hamburg (adults), Cologne (adults), Munich (children) and Dresden (adults; children) in a total of 32 participants. Concepts that emerged during the discussions were reformulated into questions/items and respective answer categories and included in the survey.

Questionnaire survey

Based on the findings of the focus groups a modular survey was constructed with questions concerning the following aspects: (i) demographic and clinical data of the patient, (ii) knowledge about half-life of current FC, (iii) attitudes towards FC (a) satisfaction with current FC, (b) expectation of new EHL products, (c) willing to switch to new EHL products, (d) required information for decision making, (e) preferred information sources, (f) facilitation of therapy in general.

Recruitment and inclusion criteria

All patients with HA or HB and caregivers of haemophilic children registered at the NMOs of the DACH Region were contacted via a letter of their NMO asking to complete the attached survey and to send it back anonymously. Patients were informed that their data would be published and that they would give automatically their informed consent by sending back the completed questionnaire. Since this survey was conducted by the NMOs, no ethical approval was requested by the ethics committees of the three countries. The systematic postal survey was sent out to 2,644 patients and parents of children with HA or HB in Germany

(January-March 2015), Switzerland (January-March 2016) and Austria (June-August 2016).

Statistical analysis

Qualitative analysis. Open questions were clustered in thematic aspects based on an inductive approach of category development [25]. The emerged clusters were then counted for their frequencies.

Quantitative analysis. All statistical analyses were conducted using the SPSS program versions 23/24 (SPSS Inc. Chicago, IL, USA). Descriptive data are shown as frequency distribution in percent or as mean ± standard deviation (M ± SD), median and range. The comparison of differences between groups was examined using univariate ANOVA, Student's *t*-test or Chi-square tests depending on the distribution of the data; *P* values <0.05 were defined as significant.

Results

Focus groups

Three out of five focus groups were conducted with 23 adult PWH (mean age 40.96 ± 17.3 years, range 19–71) and two with nine parents of children with haemophilia ranging from 4 to 19 years. From the parents (mean age 45.11 ± 5.1 years, range 39–52) 55.6% were mothers. The majority of patients had HA (81.3%), were severely affected (78.1%) and used recombinant FC (68.7%); 77.8% of paediatric and 69.6% of adult patients received prophylactic treatment. In general PWH and parents of children with haemophilia were satisfied with their current product, few complaints ($n = 6$) were mentioned due to size of package, volume, non-availability of the products when travelling, and insufficient prevention of bleeding. PWH would like to see improvement in the half-life (43.8%), package (size, completeness, logistic) (40.6%), and stability at ambient temperatures (18.8%). PWH had almost no information about up-coming EHL products, wished more information about dosing and safety, and would be willing to change FC, if the new FC shows increased benefit and a significantly increased half-life.

Postal survey

From a total of 2,644 contacted PWH with HA or HB in Germany, Switzerland and Austria 1,013 questionnaires were sent back (38.3%). Five patients had to be excluded from further analysis since they had VWD ($n = 4$), or FVII deficiency ($n = 1$). In total 1,007 questionnaires were analysed (38.1%).

Demographic and clinical data

Seven hundred forty three adult PWH and 262 parents of haemophilic children participated, two respondents could not be classified. The majority of these adult patients and parents were between 40 and 49 years old, while children were between 6 and 12 years old (Table 1).

The majority of all PWH had HA (84.5%), were severely affected (73.7%) and received regular prophylaxis (57%), mainly three times per week (47.4%), and 60.2% used recombinant FC (HA: 65%, HB: 34.2%), 14.9% of patients had an inhibitor (current or past) (Table 2).

Knowledge about half-life of current factor concentrates

Fifty-one percentage of all patients reported the correct half-life of FVIII concentrates, while only 12.4% knew the correct half-life of FIX concentrates. Comparing HA with HB patients we found that more than one quarter of patients and parents did not know the correct half-life of their current FC (HA: FVIII: 26%, HB: FIX: 31.3%) (Fig. 1).

Patients (55.1%) with severe haemophilia reported the correct half-life of FVIII compared to only 39.9% of patients with mild/moderate haemophilia (χ^2: 39.133, $P < 0.0001$).

Table 1. Demographic data of all respondents ($n = 1007$).

	All ($n = 1007$)	
Respondents*	*N*	Percentage
Haemophilia patients	743	73.9
Mothers of children with haemophilia	211	21.0
Fathers of children with haemophilia	36	3.6
Both parents together	14	1.4
Stepmother	1	0.1

	Parents ($n = 262$)		Adults ($n = 743$)	
Age categories*	*N*	Percentage	*N*	Percentage
<20 years	56	7.6	2	0.8
20–29 years	129	17.4	4	1.5
30–39 years	125	16.9	85	32.8
40–49 years	147	19.8	137	52.9
50–59 years	141	19.0	30	11.6
60–69 years	87	11.7	–	–
≥70 years	56	7.6	1	0.4

	Children ($n = 262$)	
Age categories*	*N*	Percentage
0–3 years	39	14.9
4–5 years	27	10.3
6–12 years	117	44.8
13–16 years	57	21.8
17–18 years	13	5
>18 years	8	3.1

*Missing data.

Table 2. Clinical data of haemophilia patients (n = 1007).

	Children (262)		Adults (n = 743)		∑ (n = 1007)	
Clinical data haemophilia patients*	*N*	Percentage	*N*	Percentage	*N*	Percentage
Type of haemophilia						
A	218	83.5	629	84.9	847	84.5
B	43	16.5	112	15.1	155	15.5
Severity						
Severe	193	74.5	544	73.3	739	73.7
Moderate	37	14.3	108	14.6	145	14.5
Mild	28	10.8	86	11.6	114	11.4
I don't know	1	0.4	4	0.5	5	0.5
Inhibitor						
No	217	83.1	612	85.8	830	85.1
Yes, in past	34	13.0	81	11.4	115	11.8
Yes, current	10	3.8	20	2.8	30	3.1
Type of treatment						
On demand	53	20.2	248	33.6	301	30.0
Prophylaxis	183	69.8	387	52.4	571	57.0
Switch prophy & on-demand	19	7.3	98	13.3	118	11.8
ITI	7	2.7	5	0.7	12	1.2
Frequency of prophylaxis						
Every 10–14 days	–	–	–	0.4	2	0.2
1 times per week	12	6.0	33	7.1	45	6.7
2 times per week	33	16.4	150	32.1	184	27.4
3 times per week	102	50.7	215	45.9	318	47.4
>3 times per week	54	26.9	68	14.5	122	18.2
Product category						
Plasma-derived	74	28.9	235	32.70	309	31.7
Recombinant	167	65.2	419	58.4	588	60.2
I don't know	15	5.9	64	8.9	79	8.1

*Missing data.

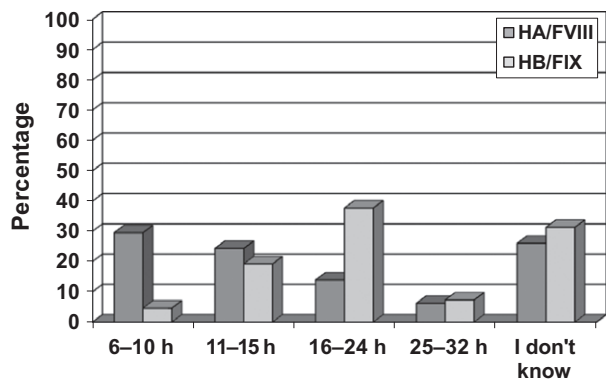

Fig. 1. Knowledge about half-life of their current factor concentrate between haemophilia A and haemophilia A patients.

Attitude towards new factor concentrates

86.6% of PWH were 'rather satisfied'/'satisfied' with their current FC (n = 845), while 9.4% were 'neither unsatisfied nor satisfied' (n = 91). Only 4% were 'rather unsatisfied'/'unsatisfied' (n = 39), mainly due to short half-life of FC (40.6%), difficult manageability (22.6%) and storage of FC in the fridge (12.3%). No differences were found between the type and severity of haemophilia.

Concerning PWH expectations of the new EHL products, a total of 1,321 responses were given by the 756 respondents. Among these aspects, less injections (55.2%), better efficacy (32.1%) and safety/no side effects (15.7%) were the most frequently mentioned (Table 3).

Table 3. Expected features from extended half-life products (n = 756).

Open answers categorized	Adults/Parents (% of respondents)
Less frequent injections	417 (55.2)
Efficacy of product	243 (32.1)
Safety of product/no side effects	119 (15.7)
Improved manageability	75 (9.9)
Better quality of life (independence, flexibility)	69 (9.1)
Extended half-life	63 (8.3)
Storage of factor concentrate at room temperature	63 (8.3)
Travel convenience	40 (5.3)
Cheaper costs	37 (4.9)
Drug tolerability	32 (4.2)
Vein protection	30 (4.0)
Different mode of administration (oral, sc)	27 (3.6)
Longer shelf-life	22 (2.9)
Once a week injection	21 (2.8)
Other aspects*	63 (8.3)

*Other aspects: <10× mentioned (availability, smaller package, bigger units, switch to prophylaxis, not tested sufficiently, etc.)

In total, 59.5% of PWH would be willing to switch to EHL products, while 36.9% were still undecided and only 3.6% were not willing to switch to a new EHL product when available on the market. Parents were more sceptical than adults; only 47.1% of parents (n = 122) would switch to new products compared to 63.8% of adult PWH (n = 464) (Fig. 2).

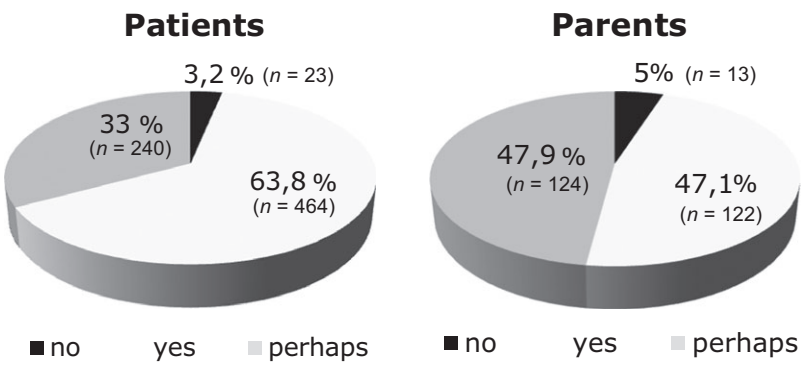

Fig. 2. Willingness to switch from current product to new extended half-life product [adult patients (n = 743), parents (n = 262)].

Reason for willingness to switch to new FC were prolonged half-life/dosing interval (87.1%), same safety of the current FC (62.8%), and if they are travel friendly (61.8%) (Table 4). Parents and adults showed significantly different preferences for stability at ambient temperatures (χ^2: 12.237, $P < 0.0001$), motivation to switch to prophylaxis (χ^2: 6.292, $P < 0.012$), beneficial for sport (χ^2: 19.805, $P < 0.0001$) and experience in practical use (χ^2: 10.100, $P < 0.001$). No difference was found for different severities.

Reasons for not willing to switch were fear of inhibitor development (71.4%) and fear of uncertain safety (60.9%). Differences between adults and parents were found for fear of inhibitor development (χ^2: 22.477, $P < 0.0001$), fear of uncertain safety (χ^2: 4.290, $P < 0.038$) and immediate availability of the current FC (χ^2: 5.092, $P < 0.024$; Table 5). The same significant differences regarding willingness to switch or not to switch were also found when comparing the different severities.

Respondents would consider changing product if the prolongation of half-life is at least double as high as the current FC (40.5%) (Fig. 3).

Significant differences were found between mild/moderate vs. severe treatment (χ^2: 17.994, $P < 0.021$),

Table 4. Reasons to switch to new extended half-life products (adult patients, parents).

Reasons for switching (multiple answers possible)	Adults *N* (%)	Parents *N* (%)	*P*-value
Longer half-life/dosing interval of new product	555 (86.7)	192 (88.9)	*ns*
More security when travelling for a short period	405 (63.3)	123 (56.9)	*ns*
Same safety of new product	392 (61.3)	146 (67.6)	*ns*
New product advantages for surgery	335 (52.3)	97 (44.9)	*ns*
Longer stability at ambient temperatures of new product	**328 (51.3)**	**81 (37.5)**	**0.0001**
Better efficacy of new product	322 (50.3)	100 (46.3)	*ns*
New product beneficial for doing sport	**285 (44.5)**	**134 (62.0)**	**0.0001**
Easier application of new product	209 (32.7)	80 (37.0)	*ns*
Lower price of new product	134 (20.9)	54 (25.0)	*ns*
Motivated to switch to prophylaxis with new product	**100 (15.6)**	**19 (8.8)**	**0.012**
Sufficient experience in practical use	**82 (12.8)**	**47 (21.8)**	**0.001**
Other reasons	28 (4.4)	13 (6.1)	*ns*

In bold are significant differences in the preference between adults and parents.

Table 5. Reasons NOT to Switch to New EHL Products (adult patients, parents).

Reasons for NOT switching (multiple answers possible)	Adults *N* (%)	Parents *N* (%)	*P*-value
Fear of inhibitor development of new product	**83 (59.7)**	**87 (87.9)**	**0.0001**
Fear of uncertain safety of new product	**77 (55.4)**	**68 (68.7)**	**0.038**
No side effects of current product	76 (54.7)	50 (50.5)	*ns*
Satisfaction with current product	68 (48.9)	36 (36.4)	*ns*
Lack of transparency of info of new product	45 (32.4)	27 (27.3)	*ns*
Good manageability of current product	33 (23.7)	17 (17.2)	*ns*
Immediate availability of current product	**33 (23.7)**	**12 (12.1)**	**0.024**
No advantage to change product	21 (15.1)	7 (7.1)	*ns*
Other reason	9 (6.5)	4 (4.0)	*ns*

In bold are significant differences in the preference between adults and parents.

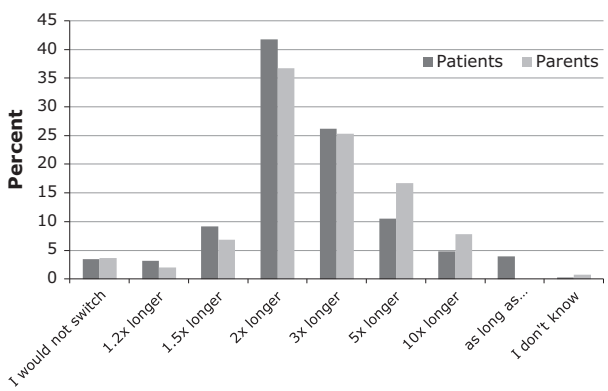

Fig. 3. Half-life prolongation time to consider switching product (adult patients, parents).

on-demand vs. prophylaxis treatment (χ^2: 18.424, $P < 0.018$) and plasma-derived vs. recombinant products (χ^2: 20.107, $P < 0.010$). No difference was found between HA and HB patients.

In order to make an adequate decision to switch PWH wished more information about half-life (84.4%), possible side-effects (81.3%) and efficacy (77%).

The majority wanted to receive information about new products from their haemophilia treater (76.3%) and the newsletter of their NMO (74.3%), followed by an information letter by their HTC/NMO (35.7%), internet (22%), patient brochure (21.3%) and NMO patient meeting (20.9%).

Facilitation of therapy in general

When asking how the therapy could be facilitated, 568 PWH mentioned in total 737 aspects. Most PWHs said that they would like to have smaller/different type of packages (33.8%), better manageability (device, syringe, etc.) (29%), different mode of administration (oral, s.c., gene therapy, permanent vein access, etc.) (19.9%), and storage at ambient temperatures (15.5%).

Differences across the countries of the DACH Region

A significant difference across the countries in the DACH Region was found concerning treatment regimen (χ^2: 44.670, $P < 0.0001$) and product category (χ^2: 30.391, $P < 0.0001$). In Germany (61.4%) and Austria (61.6%) more PWH received prophylaxis, while in Switzerland (58.3%) PWH received on-demand treatment. Whereas in Switzerland (65.2%) and Austria (67.8%) more patients used recombinant products compared to Germany (57.8%); in Germany 6% did not know which product category they used compared to 14% in Switzerland and 10.3% in Austria. Although there was a higher use of recombinant products in HA patients in all countries (DE: 62.4%, CH: 70.3%, A: 71.4%), there was a significant difference across countries (χ^2: 34.673, $P < 0.0001$).

The willingness to switch to EHL products was significantly different across countries (χ^2: 22.212, $P < 0.0001$); parents in Austria and Germany were more conservative, only 33.3% and 44% respectively were willing to switch to EHL products while in Switzerland 61.7% of parents were willing to do so (Fig. 4).

Significant differences were found as well for required information. More Germans needed information concerning side effects (χ^2: 11.987, $P < 0.002$) and supply guarantee (χ^2: 31.005, $P < 0.0001$), whereas more Swiss needed information about costs (χ^2: 19.389, $P < 0.0001$) and launch time (χ^2: 7.027, $P < 0.003$) and more Austrians about efficacy (χ^2: 9.507, $P < 0.009$).

For Germans and Swiss the most important source of information was the haemophilia treater (χ^2: 9.433, $P < 0.009$), whereas for Austrians it was the NMO newsletter (χ^2: 25.543, $P < 0.0001$). More Swiss PWH considered an information letter from the HTC/NMO (χ^2: 17.941, $P < 0.0001$) and a patient brochure (χ^2: 6.382, $P < 0.041$) as important information

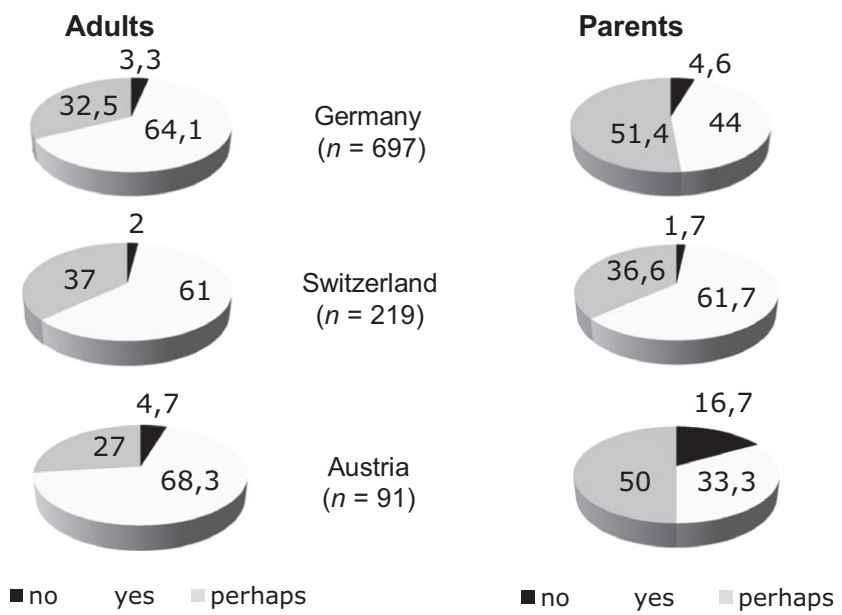

Fig. 4. Willingness to switch from current product to new extended half-life product across countries (adult patients, parents).

sources, while more Germans considered an info meeting from their HTC (χ^2: 22.350, $P < 0.0001$) as important.

Discussion

Patients from the DACH Region had limited knowledge about the new EHL FC. Even though the majority of patients were satisfied with their current FC, a significant number of patients were willing to switch to new EHL products when certain features of the products were fulfilled. Short half-life and the correlating frequent injections were the major perceived disadvantages of the current products. On the other hand patients and their parents would not compromise on safety or protection but also did not expect them to be better. Differences in the countries showed higher prophylaxis in Germany and Austria and a higher rate of recombinant FC use in Switzerland and Austria. Swiss parents were a lot more willing to switch their children to EHL products compared to the other countries. For Swiss patients pricing was an important topic while in Germany and Austria travel convenience, sufficient experience in practical use and advantages for surgery were more important.

Up to one-third of patients from the DACH Region reported not to know the half-life of their FC this result is in line with the findings of a Swedish study in which haemophilia patients had limited knowledge about their disease and treatment, and demonstrated the importance of continually providing information about haemophilia and it's treatment [26]. Canadian health care providers underlined this in their statement 'provision and uptake of disease knowledge is essential to patient self-management'. The authors claimed that PWH require the right information, from the right source, at the right time and advocated that education should be tailored to the needs of PWH [27].

Most PWH in the DACH Region expected from the new EHL products to provide less frequent injections and to be effective. Burden of frequent injections with the regular existing FC is considered one of the major obstacles to adherence in children and adults [14,15]. Although a high adherence rate was found among 397 prophylactically treated haemophilia patients (0–80 years) in Germany, the authors concluded that frequent venous punctures and time spent to inject FC lead to treatment burden and therefore to non-adherence to prophylaxis [19]. In a US discrete-choice survey preferences of PWH and willingness to pay (WTP) were assessed for on-demand, prophylaxis, and longer acting prophylaxis therapies. Dosing frequency and treatment effectiveness were considered important for treatment-related decisions. The authors concluded that the positive preferences and WTP for longer acting prophylactic therapies is likely to increase adherence and improve treatment outcomes [28]. The new, up-coming EHL products for treatment of HA and HB will possibly reduce injection frequency. Thus, these new FC may have the potential to significantly improve adherence and, consequently, to increase protection and to improve patients' quality of life [18,20–23]. No difference was found between HA and HB patients concerning their preference of the half-life extension in order to switch to new EHL products. This might be due to the fact that patients do not really have a clear concept of what half-life means and what are the potential benefits of new EHL products. On the other hand it could be interpreted that HB patients are aware of the potential benefits of FIX products having a 4–5 fold half-life extension and therefore no difference was found.

These surveys have potential limitations. The surveys were conducted at different time points; Germany participated 1 year earlier, which could have an influence on the knowledge about half-life and expectations of new EHL products. This time gap was due to the fact that the survey was initially only planned to be conducted in Germany. Only after the analysis of the data we planned to extend the survey to Switzerland and Austria in order to get a better insight of the entire DACH Region and to investigate whether there were country differences. Even if a representative number of patients were answering the survey there is always a bias if these patients are more interested and more active patients and if those patients who did not respond could show a very different picture of the situation. The interpretation of the results of the question of what half-life prolongation the product should have was very controversially discussed as around one quarter of patients did not know the correct half-life of their current product. The question arose, what did they expect from a 2 fold half-life extension? Especially, as the majority wished to have fewer injections. Would one injection less per week, what is at least achievable with every EHL product in HA and HB, be the threshold for conversion? With future surveys in this area and the findings in this survey we should deepen our understanding on treatment burden regarding the injection frequency.

We believe that there is a great need of better education of PWH regarding half-life, trough level and different options for use of EHL products. A first step into the development of educational material was the development of a neutral patient presentation and a patient brochure under the patronage of the DHG and its members of the medical advisory board.

The information gap on what PWH expect from new EHL products could be diminished at least for the DACH Region. Compared to other studies in haemophilia where in 21 European countries in total 1,400 PWH were evaluated [29], this survey with more than 1,000 PWH from only three countries depicts a quite representative picture of the real-life

situation and needs of PWH towards EHL FC in this region. Furthermore, it would be interesting to compare these findings with other European countries. PWH are interested in current and future developments of haemophilia treatment, and wish to receive information about novel therapies mainly from their treaters in the haemophilia centre and via the newsletter of their patient organisations. Therefore, the provision of adequate information about these therapies is required so that patients can make an adequate decision whether they want to change their therapy to benefit from better protection against bleeds, and a significantly reduced treatment burden. Taking a decision regarding therapy is mainly based on evidence from the literature and on patient preferences. One tool here could be the shared decision-making (SDM) process allowing patients and health care providers to make decisions collaboratively based on available evidence, and patient preferences [30].

Conclusion

In this representative survey among patients and parents of children with haemophilia of the DACH Region it could be shown that even though PWH were generally satisfied with their current FC 59.5% would be willing to switch from their current FC to the new EHL products assuming the half-life is significantly prolonged and has the same safety of the current FC. One of the most unmet needs of PWH was to reduce their treatment burden in terms of less frequent injections, besides improved manageability and better quality of life. Moreover, this survey showed new insights on how PWHs and parents want to be informed about new products, which information they require to be able to make a decision and from whom they wish to receive this information. Effective communication on the advantages and side effects of novel therapies via patient organisations and treatments centres is the basis for a sophisticated decision of the patient in the context of SDM.

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Author contributions

SvM designed the study and conducted focus groups. WM contributed to the design of the focus groups and the questions for the survey. SvM and WK developed the questions for focus groups and constructed the questionnaire for the postal survey. DHG contacted patients for focus groups; DHG, SHG/SHN and ÖHG organised shipment of postal survey and collection of questionnaires. JO, WM, MA, IP critically reviewed the data. SvM analysed the data and wrote the paper. All authors contributed to the paper and its revision.

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SvM received funding to conduct focus groups and for analysing data of the postal survey from SOBI and Baxalta/Shire. DHG and SHG received financial support to perform the patient survey (print of questionnaires, shipment of questionnaires, etc.) from SOBI; ÖHG from Baxalta/Shire. MA received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting from Baxalta/Shire, Bayer, CSL-Behring, Novo Nordisk, Octapharma, Roche, and Swedish Orphan Biovitrum. IP received occasional honoraria for lectures and advisory board session and an unrestricted grant from CSL Behring. JO received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Baxter, Bayer, Biogen Idec, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche and Swedish Orphan Biovitrum.

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References

1 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; **232**: 25–32.
2 Liesner RJ, Khair K, Hann IM. The impact of prophylactic treatment on children with severe haemophilia. *Br J Haematol* 1996; **92**: 973–8.
3 Khawaji M, Astermark J, Akesson K, Berntorp E. Physical activity and joint function in adults with severe haemophilia on long-term prophylaxis. *Blood Coagul Fibrinolysis* 2011; **22**: 50–5.
4 Gringeri A, Lundin B, von Mackensen S *et al.* A randomized clinical trial of prophylaxis in children with haemophilia a (the ESPRIT Study). *J Thromb Haemost* 2011; **9**: 700–10.
5 Manco-Johnson MJ, Abshire TC, Shapiro AD *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535–44.
6 Royal S, Schramm W, Berntorp E *et al.* Quality-of-life differences between prophylactic and on-demand factor replacement therapy in European haemophilia patients. *Haemophilia* 2002; **8**: 44–50.
7 World Federation of Hemophilia. Guidelines for the management of hemophilia. Available at http://www1.wfh.org/publications/files/pdf-1472.pdf.Accessed November 2, 2016.
8 National Hemophilia Foundation, Medical and Scientific Advisory Council. MASAC recommendation concerning prophylaxis (regular administration of clotting factor concentrate to prevent bleeding), 2007. Available at http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=57& contentid=1007. Accessed November 2, 2016.
9 Collins PW. Personalized prophylaxis. *Haemophilia* 2012; **18**(Suppl 4): 131–5.
10 Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. *Lancet* 2003; **361**: 1801–9.
11 Fijnvandraat K, Peters M, ten Cate JW. Inter-individual variation in half-life of infused recombinant factor VIII is related to pre-infusion von Willebrand factor antigen levels. *Br J Haematol* 1995; **91**: 474–6.
12 van Dijk K, van der Bom JG, Lenting PJ *et al.* Factor VIII half-life and clinical phenotype of severe hemophilia A. *Haematologica* 2005; **90**: 494–8.
13 White GC II, Beebe A, Nielsen B. Recombinant factor IX. *Thromb Haemost* 1997; **78**: 261–5.
14 Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis

therapy in haemophilia. *Haemophilia* 2001; **7**: 392–6.
15 Richards M, Altisent C, Batorova A *et al.* Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data. *Haemophilia* 2007; **13**: 473–9.
16 von Mackensen S, Wisniewski T, Urgo JC, Boggio L. Pilot test of the first hemophilia-specific burden scale for caregivers of children with hemophilia in the United States —the HEMOphilia associated CAregiver Burden scale (HEMOCAB™). *J Thromb Haemost* 2015; **13**(Suppl. 2): PO256.
17 Berntorp E. Joint outcomes in patients with haemophilia: the importance of adherence to preventive regimens. *Haemophilia* 2009; **15**: 1219–27.
18 Duncan N, Shapiro A, Ye X, Epstein J, Luo MP. Treatment patterns, health-related quality of life and adherence to prophylaxis among haemophilia A patients in the United States. *Haemophilia* 2012; **18**: 760–5.
19 Miesbach W, Kalnins W. Adherence to prophylactic treatment in patients with haemophilia in Germany. *Haemophilia* 2016; **22**: e367–74.
20 Carcao M. Changing paradigm of prophylaxis with longer acting factor concentrates. *Haemophilia* 2014; **20**(Suppl 4): 99–105.
21 Lillicrap D. Improvements in factor concentrates. *Curr Opin Hematol* 2010; **17**: 393–7.
22 Shapiro A. Development of long-acting recombinant FVIII and FIX Fc fusion proteins for the management of hemophilia. *Expert Opin Biol Ther* 2013; **13**: 1287–97.
23 Berntorp E, Negrier C, Gozzi P, Blaas PM, Lethagen S. Dosing regimens, FVIII levels and estimated haemostatic protection with special focus on rFVIIIFc. *Haemophilia* 2016; **22**: 389–96.
24 Miguelino MG, Powell JS. Clinical utility and patient perspectives on the use of extended half-life rFIXFc in the management of hemophilia B. *Patient Prefer Adherence* 2014; **8**: 1073–83.
25 Mayring P. Qualitative Content Analysis. *Forum: Qualitative Social Research* 2000. http://www.qualitative-research.net/index.php/fqs/article/view/1089/2386. Accessed March 12, 2017.
26 Lindvall K, Colstrup L, Loogna K, Wollter I, Grönhaug S. Knowledge of disease and adherence in adult patients with haemophilia. *Haemophilia* 2010; **16**: 592–6.
27 Lane S, Arnold E, Webert KE, Chan A, Walker I, Heddle NM. What should men living with severe haemophilia need to know? The perspectives of Canadian haemophilia health care providers. *Haemophilia* 2013; **19**: 503–10.
28 Chaugule SS, Hay JW, Young G. Understanding patient preferences and willingness to pay for hemophilia therapies. *Patient Prefer Adherence* 2015; **9**: 1623–30.
29 Schramm W, Gringeri A, Ljung R *et al.* ; ESCHQoL Study Group. Haemophilia care in Europe: the ESCHQoL study. *Haemophilia* 2012; **18**: 729–37.
30 Athale A, Giguere A, Barbara A, Krassova S, Iorio A. Developing a two-sided intervention to facilitate shared decision-making in haemophilia: decision boxes for clinicians and patient decision aids for patients. *Haemophilia* 2014; **20**: 800–6.

